

# Chiral thiols. Synthesis and enantiomeric excess determination

Strijtveen, Bernardus Wilhelmus Maria

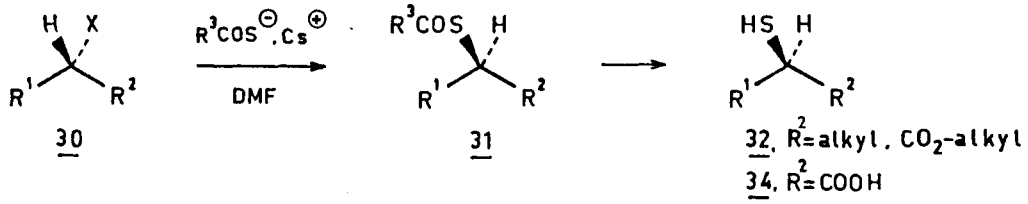
# SUMMARY

Chiral thiols are a class of chiral compounds, which is gaining more and more attention the last decennium. Especially α-mercaptocarboxylic acids are frequently found as a structural unit in (biologically) important natural products. As a consequence, many synthetic analoga or derivatives of these natural products, but also other organosulfur compounds, have been prepared. Especially interesting are the so-called pseudo-peptides. α-Mercaptocarboxylic acids often serve as the starting material for these syntheses. They are prepared synthetically, because they rarely occur in nature.

In this thesis, new systematic syntheses of mainly sec. and tert. α-mercaptocarboxylic acids and derivatives thereof are described. New methods for the enantiomeric excess (ee) determination of intermediates, the chiral thiols obtained, and chiral amines as well have been developed. Possible applications for the synthesis of some natural products are discussed.

Chapter 1 gives a short review of the development of organosulfur chemistry, of several natural and synthetic chiral organosulfur compounds, and of some general aspects of the thiol group. The work described in this thesis origines from the fact that most synthetic routes to chiral thiols suffer from problems like low yields and/or racemization.

In chapter 2 new syntheses of chiral thiols are described. These are obtained via nucleophilic substitution with cesium thiocarboxylates on the chiral substrates 30 (scheme 1). Starting from alcohols (activated as the mesylate, X=OMs), substitution with cesium thioacetate




Scheme 1

($R^3$= $CH_3$) affords the thioacetates 31 in high yields and with complete inversion of configuration. The enantiomeric excess of α-acetylthio esters (31, $R^2$= COOR) was determined with the chiral shift reagent $Eu(hfc)_3$. By combining this with the use of the natural $^{13}C$-satellites of the thioacetyl-methyl group as internal integration standard, the ee could be determined with an accuracy up to ~ 0.5%. Compared to the complementary triphenylphosphine/azodicarboxylate/thioacetic acid method, our method works equally well or better.

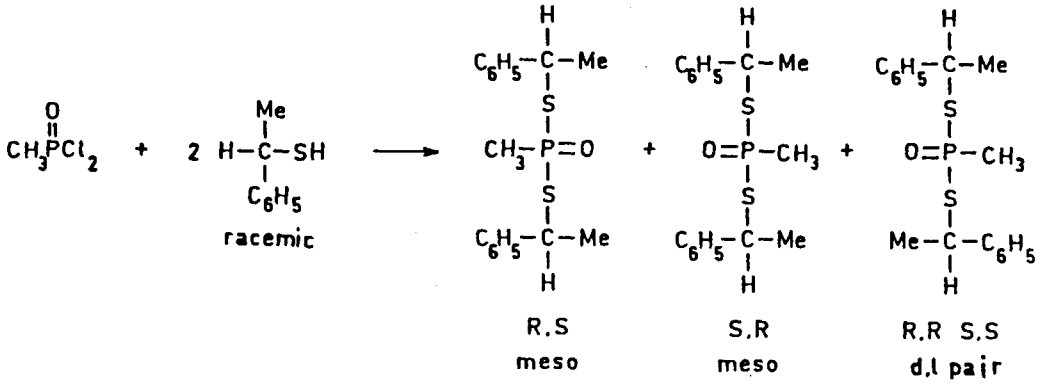
We were unable, however, to convert these racemization prone α-acetylthio esters to α-mercapto esters (34, $R^2$= COOR) or α-mercapto acids (34, $R^2$= COOH) without racemization. Different methods led, dependent on the conditions, to 5-40% racemization.

An effective, but partial solution to this problem was found in the use of the less racemization prone α-bromocarboxylic acids as starting materials. These can be obtained by diazotization of the corresponding amino acids. Substitution with cesium thiobenzoate (scheme 1, $R^3$= $C_6H_5$) followed by deprotection with ammonia or 4-chloroaniline affords in very good yields chiral α-mercaptocarboxylic acids without any racemization. A disadvantage of this method is, however, that only a few α-bromocarboxylic acids can be obtained optically pure. An effort to circumvent this limitation by direct substitution on the easily available α-hydroxy acids, leads, with the triphenylphosphine/azodicarboxylate/thioacetic acid method, to the desired α-acetylthio acids, but the enantiomeric purity is low. This appears to be caused by two different substitution routes, whether by direct substitution (with inversion) or by a double inversion (with

retention) via an intramolecular formation of an α-lactone. This is also yet another route to the interesting α-lactones in organic solution.

The succes of cesium salts in nucleophilic substitutions appears to originate mainly from their good solubility in DMF. The effect of the alkali counterion was found to be minor.

No general methods for determination of the enantiomeric excess of the chiral thiols were available. A new $^{31}$P-NMR method, based on the principles of Horeau, is described in chapter 3. The principle of this method is a "coupling" of two chiral thiols via the achiral reagent $CH_3P(=O)Cl_2$ which leads to a mixture of diastereomeric phosphonodithioates (two meso compounds and a d,l pair), see scheme 2.




Scheme 2

The $^{31}$P-NMR spectrum of this mixture shows three very well separated absorptions. The ee can be determined by integration of the signals. The method is widely applicable. A comparison with, for example, Mosher's method expresses the advantages of our method very clearly. Several

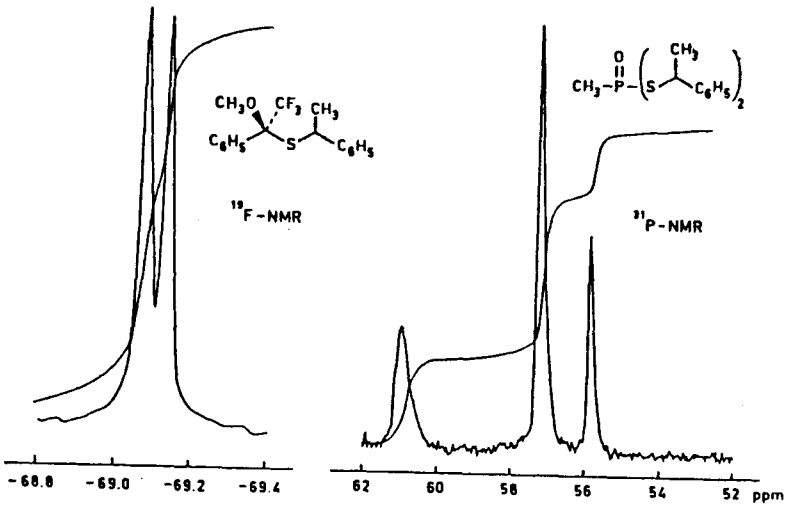


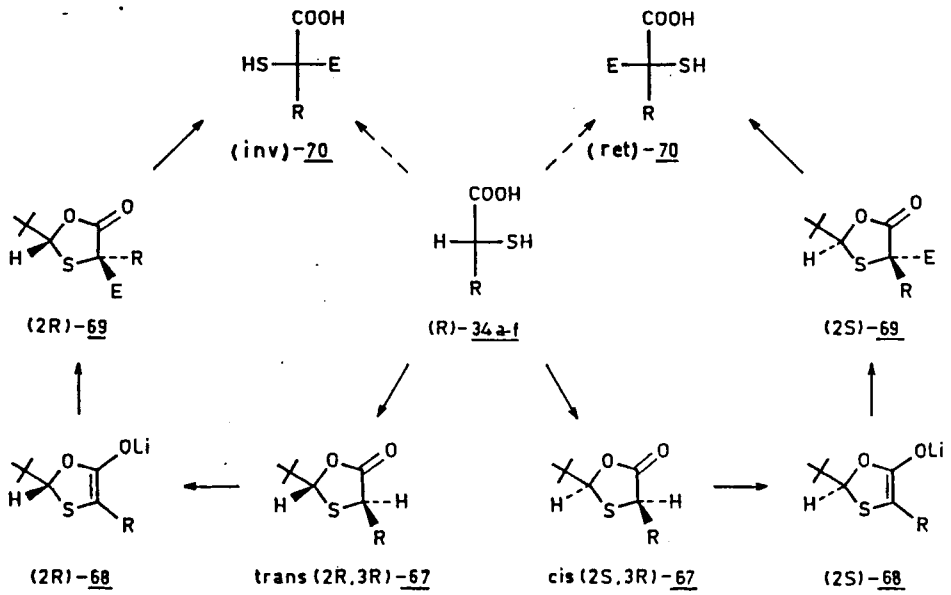

Figure 1

aspects, such as the influence of the temperature, of solvent and substituents at phosphorus but also the reason for the success of the method (no chiral recognition) are discussed.

These investigations have led also, according to the same principles, to a new $^{31}$P-method for the ee determination of chiral amines. This is described in chapter 4. $CH_3P(=S)Cl_2$ is the reagent of choice in this case. The method compares favorable with other NMR methods.

Advantages of the methods described in chapters 3 and 4 are the great signal resolution, the short reaction times (5-10 min), and no necessity for work-up. But the greatest advantage is that in contrast to all other methods no chiral auxiliary is necessary.

Chiral tert. thiols are found for example as a structural unit in some recently isolated natural products. They are, however, hardly known. A systematic synthesis of these compounds is described in chapter 5. They are obtained by stereospecific α-alkylation of chiral secondary α-mercaptocarboxylic acids, see scheme 3. The cis and trans oxathiolanones 67, obtained by




Scheme 3

acetalization of the α-mercapto acids 34 with pivaldehyde, can be separated by fractional crystallization. The cis oxathiolanones afford, after deprotonation, alkylation, and hydrolysis, the tert. α-mercaptocarboxylic acids 70 with overall retention of configuration. Trans 67 leads in the same manner to the enantiomeric series of 70 with overall inversion of configuration. The diastereoselectivities of alkylation are mostly >95%. The postulated steric course of the alkylations is proven by X-ray structures of one compound of cis 67 and two of (2S)-69 respectively. These latter two also provided an explanation of the remarkable large high field shift of the acetal proton in some compounds (2S)-69. This proton is shielded by the benzyl group, which is bent back under the thiolactone ring.

Results of alkylations with aldehydes and ketones were less satisfactory, although the diastereoselectivities were >95% in all cases. The induction on the third chiral center, in the case of aldehydes and unsymmetrical ketones was low, however: 10-30%.

The ee of the tert. α-mercaptocarboxylic acids was determined by application of the $^{31}$P-NMR method described in chapter 3.

Possible applications of this alkylation method in natural product syntheses are discussed. Further research is necessary to prove the validity of the method also in this field.